DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

348(d)

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

JUL 19 2004

Harlan Amstutz, M.D.
Joint Replacement Institute
2400 S. Flower Street
Los Angeles, CA 90007

Dear Dr. Amstutz:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your written response, dated May 17, 2004, to the noted violations and requests that you implement prompt corrective actions. William S. Vitale, Selene T. Torres, and La Nita Kelley, investigators from FDA's Los Angeles District Office, conducted the inspection from March 18 through April 13, 2004. The purpose of the inspection was to determine if your activities as a clinical investigator for the [redacted] sponsored by [redacted], complied with applicable FDA regulations. The [redacted] is a device defined in Section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate as well as to ensure that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812-Investigational Device Exemptions, Part 50-Protection of Human Subjects, and Section 520(g) of the Act [21 U.S.C. 360j(g)]. At the close of the inspection, Mr. Vitale presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. The deviations noted on the FDA 483 and our subsequent inspection report review as well as our review of your response is discussed below:

Failure to conduct the investigation according to the signed agreement with the sponsor, the investigational plan, and any conditions imposed by the Investigational Review Board (IRB). (21 CFR 812.100 and 812.110(b))

Pursuant to 21 CFR 812.100 and 812.110(b), you are required to conduct your clinical investigation in accordance with the signed agreement and the investigational plan.

Examples of your failure to satisfy this requirement include but are not limited to the following:

- At least two subjects who should have been excluded from the study because they exceeded the Body Mass Index (BMI) criteria of greater than 35 BMI, calculated as specified in the protocol, were enrolled in the study.

  If you wish to utilize exclusion criteria other than those specified in the protocol, you should contact the study sponsor before enrolling subjects under those criteria. Except in certain emergency situations, prior approval by the sponsor is required for changes or deviations from the investigational plan. FDA/IRB approval are also required if the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects. 21 CFR 812.150(a)(4).

  Your reply concerning the enrollment of subjects with a BMI >35 states that "For all future enrollments, patients with a BMI>35 will not be enrolled into the IDE study but will potentially be presented as Compassionate Use requests." We point out that there are specific requirements for compassionate use. FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition. In these circumstances, FDA uses its regulatory discretion in determining whether such use (hereinafter referred to as "compassionate use") of an investigational device should occur.

  Prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. The following Internet web site contains further information concerning compassionate use of medical devices. www.fda.gov/cdrh/ode/idepolcy.html

- You also failed to document follow-up, as specified in the protocol, one year post-operatively for two subjects [redacted]
- One subject [redacted] did not have their data submitted to the sponsor as required by the protocol. The original documentation that should have been submitted remained in the study records.
- Subject [redacted] was documented to have been evaluated during the pre-operative visit, however, forms C, D, and F were not completed at that time nor were forms D and F completed at the 6-month follow-up time period.

  Please explain what steps you have taken to assure that proper follow-up is obtained and documented as described in the study protocol.

We also note that the protocol requires the following under "Inclusion Criteria" section 4.4.1(3): "Patients for whom there is a reasonable expectation that they will be available for each examination scheduled over a two-year post-operative follow-up period and for annual examinations until the last patient entered into the study has achieved two years follow-up." It appears that many subjects you have enrolled into the study who are "out-of-the-area" (approximately 50 percent of the total study population) have been unable to obtain adequate follow-up as identified in the protocol. As a result, you should consider whether "out-of-the-area" patients should be considered for inclusion into the study given the study inclusion criteria stated in the protocol.

Failure to prepare and submit to the sponsor and the reviewing IRB complete, accurate, and timely reports of unanticipated adverse device effects occurring during the investigation as soon as possible. (21 CFR 812.150(a)(1))

Examples of your failure to satisfy this requirement include but are not limited to the following:

Three subjects experienced unanticipated device effects that were not reported to the sponsor. They are the following:

- one subject formed unusual bone lateral to the femoral neck;
- another subject experienced soft tissue catching around the hip joint; and
- a third subject experienced dislocation of his hip while rolling around in the bed.

You responded to this failure by stating that you agree to report these unanticipated device effects and you understand the importance of not reporting these and similar events in the future. This response appears to be adequate.

Failure to establish all elements of and adequately document informed consent. (21 CFR 812.100)

As a clinical investigator, you are responsible for ensuring that subject informed consent is obtained in accordance with 21 CFR Part 50. When you are obtaining informed consent, study subjects are to be provided with the information listed under 21 CFR 50.25(a) and the appropriate information listed under 21 CFR 50.25(b). Except in limited circumstances, informed consent must be documented on an IRB-approved form as described in 21 CFR 50.27.

Examples of your failure to satisfy these requirements include but are not limited to the following:

- The informed consent submitted by you and approved by your IRB failed to adequately provide all the information required. For research involving more than minimal risk, the informed consent should provide an explanation as to whether any medical treatments are available if injury occurs and, if so, what

the treatment consists of and where further information may be obtained. (CFR 50.25(a)(6))

In your written response you stated that your consent form will be changed to correct this deficiency. You also stated that you will seek IRB and sponsor approval for the revised consent form. It appears that this action, once completed, will satisfy this deficiency.

Failure to maintain accurate, complete, and current records relating to the investigator's participation in an investigation. (21 CRF 812.140(a))

Pursuant to 21 CFR 812.140(a)(3), investigators are required to maintain accurate, complete, and current records of each subject's case history and exposure to the investigational device.

Examples of your failure to satisfy this requirement include but are not limited to the following:

- Numerous case report forms reviewed contained inaccuracies or were incomplete.
    - One subject[redacted] Form D record contained no data for[redacted] and[redacted] on the form completed 10/13/03.
    - One subject's[redacted] Form D record reflecting "Limp – none" was inconsistent with the source document.
    - One subject's[redacted] height (used to determine criteria for enrollment into the study) is variably reported among Form D, Form C, and the Pre-op/Follow-up Form.
    - One subject's[redacted] source documents for the two-year post-operative visit do not contain R.O.M. data.

- Original source data supplied to the investigator on-line after November 2000 was not maintained. The data was transcribed into the database case report forms and the original source documents were not maintained. This data was reportedly submitted from out-of-the-area subjects. It was estimated that this population comprised approximately 50 percent of the study subjects. There is no way to confirm the accuracy and validity of this data.

As a clinical investigator, you are also required to maintain current records of the protocol and all correspondence with the reviewing IRB. (21 CFR 812.140(a)) However, the protocol dated September 22, 2003, was neither available at the site nor present in the regulatory binder at the time of the inspection, even though subjects had been enrolled into that portion of the investigation. Your response indicated that this protocol is and has been in the regulatory binder, but does not explain why the protocol could not be produced at the time of the inspection. Moreover, there was no documentation of IRB approval of this protocol revision.

In your written response to this letter, please provide a copy of the current protocol and consent form as approved by IRB.

In your written response submitted in May 2004, you stated that you have hired additional staff to ensure patient follow-up and data quality. In your response to this letter, please identify specific steps that have been taken to correct these deficiencies, such as training, creation and/or modification of standard operating procedures, or other similar measures.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to applicable requirements of the Act and FDA regulations.

Within 15 working days after receiving this letter please provide written documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan should include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II, HFZ-312, 2094 Gaither Road, Rockville, Maryland 20850, Attention: G. Levering Keely.

We are also sending a copy of this letter to FDA's Los Angeles District Office, and request that you also send a copy of your response to that office. If you have any questions, please contact Mr. Levering Keely by phone at 301-594-4723, ext 142.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

IRB
Harry McKellop, Ph.D. Chair **PURGED**
Research Committee/Institutional Review Board
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